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EXAMINER	
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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/582,654	ONO ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 18-26* is/are pending in the application.

4a) Of the above claim(s) *18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/4/08, 6/12/08 and 9/30/08* .
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-14 and 18-26 are all the pending claims for this application.

Election/Restrictions

2. Applicant's election of Group I (Claims 1-14 and 26) in the reply filed on 6/23/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 18-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/23/09.

4. Applicant's election without traverse of TRAIL receptor species for TRAIL-R2 and for antibody sequence species for SEQ ID NO: 8 in the reply filed on 6/23/09 are acknowledged.

5. The non-elected species of TRAIL receptor in Claim 11 and the non-elected species of antibody in Claim 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 6/23/09.

6. Claims 1-14 and 26 are the pending claims under examination.

Information Disclosure Statement

7. The IDS of 2/4/08, 6/12/08 and 9/30/08 have been considered and entered. The initialed and signed 1449 forms are attached.

8. The listing of references in the specification on p. 2 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

9. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 because Applicants have not provided sequence identifiers, e.g., at p. 17.

10. The use of trademarks, e.g., "polysorbate 80™", "TaKaRa pyrobest™", has been noted in this application. A trademark should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

11. Claims 1-14 and 26 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-14 and 26, as written, do not sufficiently distinguish over antibodies as they exist naturally because Claims 1, 14 and 26 do not particularly point out any non-naturally occurring differences between the claimed antibodies and binding compositions and the structure of naturally occurring antibodies.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-10, 12, 13 and 26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-13 and 26 are indefinite for the recitation “an antibody that “recognizes” a…(TRAIL receptor)" because the meaning of the term "recognizes” in the context of any given antibody capable of binding to the genus of TRAIL receptor family of proteins (e.g., DR4, DR5, TRID/DcR1, DcR2, OPG, TRAIL-R3, etc.) is unclear. Does this mean that the genus of antibodies encompassed by the claim, are cross-reactive with or amongst the family of all TRAIL receptors? The ordinary artisan cannot determine the boundaries of the product invention because no single antibody capable

of specifically binding to a single known TRAIL receptor, e.g., TRAIL-R2, is defined by the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

13. Claims 1-13 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using apoptosis-inducing TRAIL-R2 antibodies in vitro for cancer cells or in vivo for animal cancer models, does not reasonably provide enablement for using any antibody in vivo to induce apoptosis in any human cancer subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1 and 11 are interpreted as being drawn to an antibody that binds TRAIL-R2 (DR5). Claims 12 and 13 depend from Claim 1 and are drawn to the antibody having the ability to induce apoptosis (Claim 12) in any cancer cell (Claim 13). Claim 26 is drawn to the pharmaceutical composition comprising the antibody of Claim 1. All the remaining and dependent claims fall under the rejection. The claims are examined for an implied intended use of inducing apoptosis in any cancer cell in vitro much less vivo including occurring within a human subject.

The relative skill in the art is a Ph.D. or M.D. with a background in immunotherapeutics.

Disclosure in the Specification

The working examples of cytotoxic, apoptosis-inducing TRAIL-R2 antibodies are described in Section 4 (pp. 40-41) of the specification:

The data for cytotoxic activity of TRAIL-R2 diabodies on COLO 205 cancer cells in vitro are shown in Fig. 1. The cell count did not decrease after addition of the diabody alone, suggesting that the diabody has no cytotoxic activity by itself, and cytotoxic activity was detected when M2 antibody was added to crosslink the diabody. This suggests that apoptotic signals are transmitted when the polymerization of TRAIL receptor on the surface of cell membranes is enhanced.

The data for cytotoxic activity of TRAIL-R2 triabodies on COLO 205 cancer cells in vitro are shown in Fig. 2. The results showed that neither the diabodies nor whole IgG had marked cytotoxic activity. In contrast, the cell count was dramatically decreased

after addition of the triabody, suggesting that the triabody had obvious cytotoxic activity with the activity significantly higher when the triabody had the 1-mer or O-mer linker.

The data for cytotoxic activity compared between the triabody and tandem diabody on COLO 205 cancer cells in vitro are shown in Fig. 3. This result showed that the activity of the tandem diabody was stronger than that of the triabody, and was equivalent to or greater than that of the natural ligand Apo2L. These results suggest that of the molecules tested, the tandem diabody by itself is the most effective molecule.

Applicants have demonstrated that different multivalent forms of a TRAIL-R2 antibody can produce vastly different cytotoxicity profiles within the same cancer cell in vitro. Applicants contemplate using this as a method of treatment for tumors in being formulated into pharmaceutical compositions. None of the working examples demonstrate a relevant animal disease model correlate considering the TRAIL-R2 antibody effects on mediating apoptosis on a tumor target cell in vivo. The specification does not disclose whether the method is effective in animals with a pre-existing TRAIL-R2-expressing tumor, and this is a significant omission in view of the well-known immunosuppressive effects of certain tumors. The criticality of a working example encompassing intended in vivo effects, especially inducing apoptosis in a pre-existing neoplasia is a significant omission especially in view of the status of the field. Therefore, it appears that undue experimentation would be required of one skilled in the art to practice the instant invention using the teachings of the specification alone and the specification fails to enable the use of anti-TRAIL-R2 antibodies for tumor therapy in vivo via induction of apoptosis.

Prior Art Status: TRAIL-R2 antibodies have some in vivo applicability for inducing apoptosis in cancers

Yagita et al. (Cancer 95:777-783 (10/2004)) provides an overview of immunotherapeutics for TRAIL-R2 (DR5) at the time of application filing and beginning on p. 779, Col. 1, describes anti-human DR5 antibodies having been shown to induce apoptosis in melanoma cell lines in vitro, and the TRA-8 (DR5) antibody of Ichikawa (discussed below) inducing tumoricidal activity in mouse xenografts. Yagita discuss the status of immunotherapeutics stating:

> "The potential toxicity in pathological conditions may also be a concern as discussed with rTRAIL. A recent study has shown that the anti-tumor effects of anti-human DR5 Mabs were synergistically enhanced in vitro by combination with chemotherapeutic drugs such as adriamycin and cisplatin. However, the potential toxicity in the combination therapy is again a concern, as discussed for rTRAIL. Although the potential toxicity remains to be determined, Human Genome Sciences and Cambridge Antibody Technology are now planning to initiate a phase I clinical trial of an agonistic humanized anti-DR5 mAb (HGS-ETR2) in patients with advanced tumors in the UK" (p. 780, Col. 1, ¶1).

> "Therefore, anti-DR5 mAb may be more beneficial than rTRAIL for cancer therapy, because it not only primarily eliminates most TRAIL-sensitive tumor cells at the time of administration, but also secondarily induces tumor specific effector and memory T cells that can eradicate even TRAIL-resistant tumor variants and provide long-term protection from tumor recurrence" (p. 780, Col. 1, ¶2).

Wakalee et al. (Ann. Oncol. On-line publication 7/24/09) reports on the phase I results for the HGS-ETR2 antibody mentioned in Yagita showing that the antibody represent a novel approach to treating solid tumors disclosed in Table 1 (***NSCLC, soft tissue sarcoma, prostate, renal, NHL and breast***). Of twenty-seven patients, stable disease was seen in 9 patients with a variety of tumor types. The phase I study of the

antibody every 21 days documented disease stability in 12 of 37 patients and the study establishes a single agnet does of HGS-ETR2 where the future development should focus on better identification of patients and on combination regimens. Further, detection of TRAIL-R2 by immunohistichemistry has not correlated with response to the agent in preclinical models, so effects to detect other markers that may more accurately predict response should be considered.

Ichikawa et al. (Nat. Med. 7:954-960 (2001)) teach that the anti-TRAIL-R2 Mab, TRA-8, was tumoricidal for ***human astrocytoma cell line, 1321N1, and human leukemic Jurkat cell line*** in SCID mice (Fig. 4), suggesting that TRA-8 is a potent inhibitor of in vivo tumor-cell growth, and that the inhibition is mediated by apoptosis.

Miller et al. (WO 01/77342; published 10/18/01; cited in the IDS of 9/30/08) discloses in Figures 12A-E apoptosis induced by an anti-DR5 tetravalent antibody (16E2 Octopus), an anti-DR5 bivalent IgG antibody (16E2 IgG), and Apo2L/TRAIL (Apo2L) on cancer cell lines: COLO 205 (Fig. 12A), SK-MES-1 (Fig. 12B), HCT116 (Fig. 12C), and HOP 92 (Fig. 12D), compared to a non-cancer control cell line, HUMEC (Fig. 12E); Figure 14 represents the *in vivo* activity of Apo2L/TRAIL (60mg/kg, 5x/week), 3H3 bivalent IgG (5mg/kg given days 0, 3, 5 and 9), 16E2 bivalent IgG (16E2) (5mg/kg given days 0, 3, 5 and 9), and 16E2 Octopus (5mg/kg given days 0, 3, 5 and 9) with respect to ***COLO 205*** tumors in athymic nude mice; and Figure. 15 represents an alamarBlue in vitro assay confirming the apoptotic activity of the material used in the mouse studies (Apo2L/TRAIL and 16E2 Octopus) as compared to an Apo2L standard positive control.

Under MPEP 2164.02 ("Working Example"): The issue of "correlation" is related to the issue of the presence or absence of working examples. "Correlation" as used herein refers to the relationship between in vitro or in vivo animal model assays and a disclosed or a claimed method of use. An in vitro or in vivo animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention. If there is no correlation, then the examples do not constitute "working examples." In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995).

Thus for at least human colon cancer cells, *COLO 205*, Applicants own working examples and the working examples in the prior art demonstrate that antibody-targeting of TRAIL-R2 in human colon cancer is achievable and can mediate an apoptotic endpoint in the cancer cell whether in vitro or in vivo. Additionally, the HGS-ETR2 antibody and the TRA-8 antibody each appear to be successful in some in vivo cancer therapy animal models.

Unpredictability/ Undue Experimentation

Therefore, due the unpredictability of immunotherapeutics in general, and in view of the insufficient guidance and/or working examples concerning the use the claimed antibodies as immunotherapeutic agents, one skilled in the art would not know how to practice the broadly claimed invention, i.e., administer anti-TRAIL-R2 antibodies for the apoptosis inducing effect in any cancer cell and its accompanying pathologies without undue experimentation.

Enablement

14. Claims 1-13 and 26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using apoptosis-inducing TRAIL-R2 antibodies comprising the full VH CDRs and the full VL CDRs from a parent TRAIL-R2 antibody, does not reasonably provide enablement for antibody fragments having less than the full complement of CDRs or single variable domain antibodies from any TRAIL-R2 antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims,

the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention/ Skill in the Art

Claims 1 and 11 are interpreted as being drawn to an antibody that binds TRAIL-R2 (DR5). Claims 2-5, 9 and 10 are interpreted as being drawn to the features of the anti-DR5 antibody, where the antibody is a minibody (or as defined in the specification as an antibody fragment) (Claim 2), or comprises 3 or more antigen binding sites (Claim 3) or comprises three antigen binding sites (Claim 4), or comprises three scfvs forming a trimer (Claim 5), or comprises four antigen binding sites (Claim 9) or comprises four variable regions forming a dimer (Claim 10). Accordingly, the claims are examined as encompassing antibody fragments comprising less than the full complement of VH and VL CDRs and even as single domain antibodies.

The relative skill required to practice the invention is a molecular immunologist.

Disclosure in the Specification

The specification teaches working examples of making and using diabodies, triabodies and tandem diabodies starting from the parent antibody, KMTR1. All of the working examples comprise the VH CDRs and VL CDRs from the parent molecule, and none comprise a single variable domain of VH or VL. The claims are not limited to describing the physical structure of the antibody antigen binding domain, only that it recognize a TRAIL-R2 molecule, and which meaning of the term “recognizes” is not defined by specificity, affinity or avidity for the particular target protein. The specification

does not enable any molecules that do not have a hinge or that are modified in protein sequences or scFV that have only one CDR of a heavy and light chain.

The claims are not commensurate in scope with the enablement provided in the specification. The specification does not support the broad scope of the claims which encompass modified forms of the antibody variable domains, for example, the general tolerance to modification and extent of such tolerance; the specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical; and The specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any sized fragment made of any aspect of the VH or VL domain in whole or in part. The scope of the claims must bear a reasonable correlation with the scope of enablement. See In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the protein's structure and still maintain biological activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F,2d 1200, 18 USPQ 1016 (Fed. Cir. 1991) at 18 USPQ 1026 1027 and Ex parte Forman, 230 USPQ 546 (BPAI 1986).

Prior Art Status: Binding specificity for single CDR-domain antibodies is unpredictable

Applicants' specification is deficient in its disclosure of the full scope of the claimed invention and does not provide sufficient guidance for even the most skilled artisan to practice making and using the breadth of antibodies encompassed by the claims absent undue experimentation.

MacCallum *et al.* (J. Mol. Biol. (1996) 262:732-745; cited in the IDS of 9/30/08), analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right col) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left col.).

De Pascalis *et al.* (The Journal of Immunology (2002) 169, 3076-3084; cited in the IDS of 9/30/08) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right col.). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left col.).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site, is underscored by Casset *et al.* ((2003) BBRC 307, 198-205; cited in the IDS of 9/30/08), who constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design, and the peptide was designed

with 27 residues formed by residues from 5 CDRs (see entire document). Casset *et al.* also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left col.) and this is demonstrated in this work by using all CDRs except L2 and a framework residue located just before the H3 (see page 202, left col.).

Vajdos *et al.* ((2002) J. Mol. Biol. 320, 415-428; cited in the IDS of 9/30/08), additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left col.).

Holm *et al* ((2007) Mol. Immunol. 44: 1075-1084; cited in the IDS of 9/30/08) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract).

Chen *et al.* (J. Mol. Bio. (1999) 293, 865-881; cited in the IDS of 9/30/08) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866).

Wu *et al.* (J. Mol. Biol. (1999) 294, 151-162; cited in the IDS of 9/30/08) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that

accompany antigen binding (page 152 left col.) but certain residues have been identified as important for maintaining conformation.

Thus, while one can make the statement that a single CDR makes a significant contribution in the antigen binding, the residues in these CDRs are not the only residues that influence binding and in fact the prior art as well as applicants own disclosure do not support that it was clearly established, that the a single CDR domain alone is sufficient to define the binding specificity of any antibody for any antigen, much less that multiple antibodies can predictably be generated having the same binding specificity based on a single CDR region (or less than full complement of VH and VL CDRs).

Additionally, the data seem to indicate that it is the frameworks and CDRs that contribute to antigen binding. Further, there are no examples of mixing or matching of the light chain CDRs or heavy chain CDRs and most importantly there is no example of placing a single CDR domain of a heavy chain and/or a light chain in just any framework and producing an antibody that binds antigen as broadly claimed or suggested.

Prior Art Status: Binding specificity for single domain antibodies is unpredictable

The single domain antibodies taught in WO 2004/003019 (Domantis) and Ward et al. (Nature 341:544-546 (1989))) appear to be examples of single domain antibodies generated against a limited number of antigens that have been shown to retain antigen binding specificity. However, by and large, the art recognizes that single domain antibodies do not provide the sufficient contact sites for antigen binding.

Smith-Gill et al. (J. Immunol. 139:4135-4144 (1987)) observed from chain recombination experiments that through interactions between the VH/VL pair, specificity

for antigen is H chain determined, specific binding is increased when L chains of the same parental isotype are used, and that both H and L chains determine fine specificity.

Kumar et al. (J. Biol. Chem. 275:35129-35136 (2000)) discloses Fab molecules with anti-DNA (light chain) and anti-cardiolipin (heavy chain) binding activities, and that pairing of the partner chains is dependent on the particular H/L chain pairing.

Song et al. (Biochem Biophys Res Comm 268:390-394 (2000)) discloses that affinity and specificity of scFv for preS1 protein of HBV is dependent on S-S bond formation in conferring correct refolding of the fragments for retaining binding properties, and that L chains are predominant in antigen binding.

Therefore, selecting and producing just any variable domain substituted antibody with the ability to properly associate and assemble into a fully functional antibody which maintains the binding specificity for the original antigen would be highly unpredictable based on the methods described in the specification and the prior art disclosures.

Unpredictability/ Undue Experimentation

The specification provides no direction or guidance regarding how to produce the genus of chimeric antibodies as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Dufner (Trends Biotechnol. 24(11):523-29 (2006)) teaches: "specific structural information - on the antibody to be optimized, its antigen and their interaction- is rarely available or lacks the high resolution required to determine accurately important details such as side-chain conformations, hydrogen-bonding patterns and the position of water molecules" (p. 527, Col. 2, ¶1). Applicants

specification and the evidence of record does not define specific structural information detailing the number of and exact position of hotspots in the CDRs which “can vary considerably from case to case and therefore cannot be predicted" (legend to Figure 2 of Dufner). Thus even with the availability of screening approaches as taught in the specification and Dufner, the ordinary artisan could not predict the hotspots much less those residues critical for conferring specific TRAIL-R2 antigen binding for any claimed antigen binding domains absent further additional information and experimentation. What does a sequence alignment for the CDRs look like for a "reasonable" number of TRAIL-R2 antibodies that would guide the ordinary artisan in determining the important common shared or similar binding residues that confer specific antigen binding? Are any hotspots present in the CDRs, what is the frequency of those hot spots and what are the positions of those hot spots?

Thus while the level of skill required to generate the TRAIL-R2 antibodies is that of a molecular biologist or molecular immunologist, the artisan of ordinary skill in the art would have been required to characterize the parent antibody, identify candidate amino acid residues for substitution in the FR and/or CDR domains, perform the mutagenesis on the FR and CDR domains, produce and express the chimeric antibodies, measure binding characteristics (e.g., binding specificity, equilibrium dissociation constant (K_D), dissociation and association rates (K_{off} and K_{on} respectively), and binding affinity and/or avidity compared with the parent antibody), and then finally perform bioassays to identify any one or more of the characteristics of an antibody. The technology to perform these experiments was available at the time of application filing, but the amount of

experimentation required to generate even a single FR- and/or CDR-modified chimeric antibody meeting all of the claim limitations would not have been routine much less could one of ordinary skill in the art predict that any one or combination of all the CDR region substitutions encompassed by the claims would result in *just any* chimeric antibody clone having retained antigen binding activity for the original antigen (MPEP 2164.06, "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (In re Wands, 858 F.2d 731, 737, 8 USQP2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Priority

15. For purposes of applying art, Applicant cannot rely upon the foreign priority paper, i.e., JP 2003-415735 (filed12/12/2003) to overcome the art rejection(s) because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15. Accordingly, for purposes of applying art, the instant claims are given the priority filing date of *12/10/04*.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

16. Claims 1, 11 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by van Geelen et al. (Br J Cancer. 2003 Jul 21; 89(2):363-73); cited in the PTO 892 form of 5/26/09).

Claims 1 and 11 are interpreted as being drawn to an antibody that binds TRAIL-R2 (DR5). Claim 26 is drawn to the pharmaceutical composition comprising the antibody of Claim 1.

van Geelen teaches the TRAIL-R2 antibody, huTRAIL-R2-M413 (M&M, p. 365, Col. 1, ¶1).

17. Claims 1, 11-13 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohtsuka et al. (Oncogene 22:2034-2044 (2003 Apr 3); cited in the PTO 892 form of 5/26/09).

The interpretation of Claims 1, 11 and 26 are discussed above under section 16. Claims 12 and 13 depend from Claim 1 and are drawn to the antibody having the ability to induce apoptosis (Claim 12) in a cancer cell (Claim 13).

Ohtsuka teaches an agonistic anti-human DR5 monoclonal antibody, TRA-8, which induces apoptosis of most TRAIL-sensitive tumor cells both in vitro and in vivo, and which synergizes with chemotherapy agents with the capability of inducing DNA damage, such as Adriamycin and Cisplatin, to enhance antibody-induced apoptosis of several types of human tumor cells (Fig. 1, 2; Table 1).

18. Claims 1, 11-13 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Ichikawa et al. (Nat. Med. 7:954-960 (2001)).

The interpretation of Claims 1, 11 and 26 are discussed above under section 16, and for Claims 12 and 13 under section 17.

Ichikawa teach that the anti-TRAIL-R2 Mab, TRA-8, was tumoricidal for human astrocytoma cell line, 1321N1, and human leukemic Jurkat cell line in SCID mice (Fig. 4), suggesting that TRA-8 is a potent inhibitor of in vivo tumor-cell growth, and that the inhibition is mediated by apoptosis.

19. Claims 1-5, 9-13 and 26 are rejected under 35 U.S.C. 102(e) as being anticipated by Li et al. (US 20080248037; published 10/9/08; priority to 4/6/04).

The interpretation of Claims 1, 11-13 and 26 is discussed above under sections 16 and 17. Claims 2-5, 9 and 10 are interpreted as being drawn to the features of the anti-DR5 antibody, where the antibody is a minibody (or as defined in the specification as an antibody fragment) (Claim 2), or comprises 3 or more antigen binding sites (Claim 3) or comprises three antigen binding sites (Claim 4), or comprises three scfvs forming

a trimer (Claim 5), or comprises four antigen binding sites (Claim 9) or comprises four variable regions forming a dimer (Claim 10).

Li teaches antibodies that bind DR5 receptors, and the antibody is in monomer, dimer, trimer, tetramer, or higher oligomeric forms or the antibody is a chimeric molecule or fusion protein comprising the antibody fused to a heterologous peptide sequence facilitating the formation of oligomeric complexes. The antibody inhibits the interaction of Apo-2L with DR5 receptor or the antibody is an agonist of at least one Apo-2L associated biological activity, for example, the induction of apoptosis via the DR5 receptor [0015]. Li teaches “Antibody fragments" comprise a portion of an intact antibody, preferably comprising the antigen-binding or variable region thereof. Examples of antibody fragments include Fab, Fab’, $F(ab')_2$, and Fv fragments; diabodies; linear antibodies; single-chain antibody molecules; and multispecific antibodies formed from antibody fragments [0075]. Li shows in Example 7 the DR5 antibody results from in vitro AlmarBlue bioassay using human colon carcinoma cells as targets that the antibody induced inhibition of cell proliferation via apoptosis. Li claims the antibody where the heavy chain and the light chain are connected by a flexible linker to form a single-chain antibody such as scFv antibody.

20. Claims 1-13 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller et al. (WO 01/77342; published 10/18/01; cited in the IDS of 9/30/08).

. The interpretation of Claims 1-5, 9-13 and 26 is discussed above under sections 16-18. Claims 6-8 are interpreted as being drawn to the linker for the scfv of Claim 5

having 0 to 2 amino acids (Claim 6), or 0 amino acids (Claim 7) or 1 amino acid (Claim 8).

Miller discloses in Figures 12A-E apoptosis induced by an anti-DR5 tetravalent antibody (16E2 Octopus), an anti-DR5 bivalent IgG antibody (16E2 IgG), and Apo2L/TRAIL (Apo2L) on cancer cell lines: COLO 205 (Fig. 12A), SK-MES-1 (Fig. 12B), HCT116 (Fig. 12C), and HOP 92 (Fig. 12D), compared to a non-cancer control cell line, HUMEC (Fig. 12E); Figure 14 represents the in vivo activity of Apo2L/TRAIL (60mg/kg, 5x/week), 3H3 bivalent IgG (5mg/kg given days 0, 3, 5 and 9), 16E2 bivalent IgG (16E2) (5mg/kg given days 0, 3, 5 and 9), and 16E2 Octopus (5mg/kg given days 0, 3, 5 and 9) with respect to COLO 205 tumors in athymic nude mice; and Figure. 15 represents an alamarBlue in vitro assay confirming the apoptotic activity of the material used in the mouse studies (Apo2L/TRAIL and 16E2 Octopus) as compared to an Apo2L standard positive control. Miller discloses polypeptide chains such as scfv comprising the VH and VL domains linked by an amino acid X1 or X2 of 0 to 1 residues (p. 14, lines 1-4); or 2 to about 10 amino acid residues, and most preferably four or less residues (p. 30, lines 32-33).

List of 35 U.S.C. 102 Art References Cited in IDS

21. The following references were cited in the IDS' of record and are considered proper 102(a) or (b) art as applied to generic Claims 1, 11 and 26. Because of the extensive number of references in the TRAIL-R2 (synonyms are, e.g., DR5, KILLER,

TRICK2, CD262 or ZTNFR9) antibody art field, these references are only summarized for purposes of brevity:

KIRIN BEER KABUSHIKI KAISHA (EP 1396500; published 3/10/04; cited in the IDS of 9/30/08) under 102(a): teaching TRAIL-R2 antibodies having in vitro apoptosis-mediating effects in cancer cells;

Mori et al. (Cell Death & Different., On-line publication 10/24/03; cited in the IDS of 9/30/08) under 102(a): teaching mAbs to TRAIL-R2 induced apoptosis in several human cancer cells in vitro (and as applied to instant Claims 12 and 13);

Walczak et al. (EMBO J. 16(17):5386-5397 (1997); cited in the IDS of 9/30/08) under 102(b): teaching anti-TRAIL M180 Mab specifically inhibiting TRAIL-R2;

Bodmer et al. (Nat Cell Biol. 2:241-243, 2000; cited in the IDS of 9/30/08) under 102(b): teaching rabbit polyclonal anti-TRAIL-R2 antibody;

Ashekenazi et al. (WO 00/75191; published 12/14/00; cited in the IDS of 9/30/08) under 102(b): teaching anti-DR5 receptor antibody;

Buchsbaum et al. (Clin. Can. Res. 9:3731-3741 (9/1/03); cited in the IDS of 9/30/08) under 102(a): teaching TRA-8 antibody for DR5;

Griffith et al. (J. Immunol. 162:2597-2605 (1999); cited in the IDS of 2/4/08) under 102(b): teaching TRAIL-R2 antibody having apoptosis inducing ability in melanoma cells (and as applied to instant Claims 12 and 13); and

Mori et al. (WO 02/094880; published 11/28/02; cited in the IDS of 2/4/08) under 102(b): teaching TRAIL-R2 antibody induced apoptosis in several human cancer cells in vitro (and as applied to instant Claims 12 and 13).

Conclusion

22. No claims are allowed.

23. The antibody of amino acid sequence of SEQ ID NO:8 is free from prior art.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LYNN BRISTOL whose telephone number is (571)272-6883. The examiner can normally be reached on 8:00-4:30, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/
Examiner, Art Unit 1643
Temporary Full Signatory Authority